REMARKS

Claims 3 and 5-15 are pending. All of the pending claims are rejected. Applicants submitted a Pre-Appeal Brief Request for Review on October 28, 2008. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed from the USPTO on December 10, 2008. A panel of three Examiners including the Supervising Primary Examiner of the art unit maintains the rejection of all of the pending claims. No further details are provided nor are any reactions provided to the arguments and explanations that Applicants submitted in the Pre-Appeal Brief Request for Review filed on October 28, 2008. Applicants submit herewith a Declaration pursuant to 37 C.F.R. §1.132 of Michel Aigle, Ph.D.

Rejection under 35 USC 103

As Applicants previously explained, the presently claimed invention is a method for evaluating the efficiency of a sterilization process whereas Safar *et al.* teach methods to study the thermal stability and conformational transitions of scrapie amyloid protein and their correlation with infectivity. The Examiner acknowledges that the current claims are drawn to a method of subjecting a prion protein to a degradation indicator and determining the level of degradation thereof. The Examiner alleges that Safar *et al.* teach the same method step since Safar *et al.* teach a method of subjecting a scrapie amyloid protein, which is a prion, to thermal exposure and evaluating the inactivity of the treated prion protein. Thus, the Examiner alleges that the process of Safar *et al.* is substantially similar, if not identical, to the presently claimed method. The Examiner also disagrees with Applicants' explanations that the yeast prion proteins of the current invention are not analogs of their mammalian counterpart, and that there is no teaching, motivation or suggestion to substitute the prion protein of Safar *et al.* with a yeast prion. The Examiner considers that since yeast proteins are recognized as "prion proteins" and known as analogs of the mammalian counterpart in the art, it would have been obvious to one of ordinary skill in the art to try the yeast prion proteins in the place of mammalian prion proteins.

1. <u>The references when combined do not teach or suggest the presently claimed methods.</u>

A. Regarding measuring degradation

Applicants submit that the references, when combined, do not produce the presently claimed methods. As such, the Examiner has failed to set forth a proper *prima facie* case of obviousness. Applicants respectfully reiterate that the goal of ***Safar et al.*** was to ***study the thermal stability and conformational transitions of scrapie amyloid protein and its correlation with infectivity***. To this end, Safar *et al.* submitted a scrapie amyloid protein to heat treatment and to chemical scrapie inactivators such as FA, SDS, additional α-helix-inducing fluorinated alcohols and TFA to measure their effect on the conformation of PrP27-30 and the ability to propagate, replicate and cause disease. One of ordinary skill in the art would agree that analyzing the results of Safar *et al.*, particularly Figure 1 where the effect of heat and formic acid on PrP27-30 is visualized by silver staining and Western blot, reveals that Safar *et al.* only demonstrate a conformational transition of scrapie amyloid protein which they correlate with a reduction in infectivity. ***Safar et al. do not teach or suggest the degradation of a prion protein***. On the contrary, the protein level visualized by silver staining and Western blot reported by Safar *et al.* is clearly not changed. (See, Fig. 1) Therefore, ***Safar et al. do not measure degradation***. Rather, ***Safar et al. measure a conformational change*** which they correlate with the infectivity level of the prion. Safar *et al.* do not make a correlation between the infectivity level of the prion and its degradation.

The presently claimed method is for evaluating the efficiency of a sterilization process. Since some sterilization processes allow a significant degradation of prion proteins whereas other methods produce a weaker degradation, the method claimed in the present application allows the evaluation of the efficacy of different sterilization processes. ***The presently claimed methods measure***, when using for example ozone, a powerful sterilizing agent, the ***destruction or degradation of a yeast prion.*** Figure 4 of the present specification demonstrates that the prion protein is degraded as no band is observed in the "T" lane on the Western blot. Applicants respectfully submit that for a similar experimental protocol, following the reasoning of the Examiner, a degradation of the prion protein should be observed in Figure 1 of Safar *et al.* That is, degradation of the prion protein should normally be observed as a decrease in the intensity of bands observed in a Western blot. However, contrary to the Examiner's position and contrary to what would be expected if degradation of the prion protein was in fact occurring, degradation is not demonstrated in Figure 1 of Safar *et al.*

To further explain these basic differences, Applicants direct the Examiner to the Declaration pursuant to 37 C.F.R. §1.132 of Michel Aigle, Ph.D, submitted herewith as Exhibit A. Therein, the Declarant under penalty of perjury explains that the methods of the present invention measure and validate the absence of residual yeast prion proteins to confirm the efficacy of the sterilization procedure. This is demonstrated by different analytical methods, among them a Western blot experiment. (*See*, Aigle Declaration, paragraph 6)

To the contrary, Safar *et al.* demonstrate that after thermal treatment, the conformation of prion protein is changed having less infectivity. This is demonstrated by classical Western blots. Applicants submit that one of ordinary skill in the art understands that Western blots are not well equipped to demonstrate conformation changes. (See, Aigle Declaration, paragraph 7) Only in some instances may Western blots suggest conformational changes. Figure 1 of Safar et al. demonstrates that the prion proteins are present in about the same quantities both before and after treatment. Safar et al. do not demonstrate nor do they suggest physical destruction of prion proteins. (See, Aigle Declaration, paragraph 7)

B. Regarding replacing mammalian prion proteins with yeast prion proteins

The Examiner maintains that yeast prions are known as mammal prion analogs and thus it would have been obvious to replace the mammalian prion disclosed in Safar *et al.* by a yeast prion. Applicants refer to the Declaration under 37 C.F.R. 1.132 submitted on August 28, 2008 by Dr. Belhumeur, an inventor of the present invention, in order to evidence the contrary. Applicants submit that one or ordinary skill in the art would agree that there are ***significant differences between yeast prion proteins and mammalian prion proteins***. Even though there may be some belief among some scientists that yeast proteins are analogs of "prion proteins" and known as analogs of mammalian prions, there is still significant uncertainty regarding whether one of ordinary skill in the art could predict the utility of an invention based upon the teachings of Safar *et al.* using the proteins disclosed by Coustou *et al.*, Glover *et al.* or Wickner *et al.*

2. The Examiner rejects claims 3 and 5-15 as allegedly unpatentable over Safar *et al.*, *Protein Science*, 1993, 2:2206-2216 in view of Coustou *et al.*, *PNAS* (1997), Glover *et al.*, *Cell* (1997) or

Wickner, *Science* (1994). Applicants respectfully traverse. Claim 9 is patentable under 35 USC 103(a) over Safar *et al.* in view of Coustou *et al.*, Glover *et al.* or Wickner *et al.*

Applicants respectfully submit that the methods of claims 3 and 5-15 are not obvious over Safar *et al.* in view of Coustou *et al.*, Glover *et al.* or Wickner *et al.* for the reasons set forth above. Additionally, the presently claimed methods provide significant advances over the prior art. The presently claimed methods may be adapted to industrial processes having a need to control the efficiency of a sterilization process. By Western Blot analysis, the present specification demonstrates that there is no residual yeast prion protein detectable after ozone treatment. (See, e.g. Table 1 of the instant specification; Aigle Declaration, paragraph 6) Ozone treatment goes beyond all the treatments described by Safar *et al.* as ozone is an extremely powerful oxidative process, able to break down chemical bonds. The mere fact of knowing, from Safar *et al.* that heat or chemical treatment may have an effect on the conformation of a mammal prion protein is not sufficient to suggest to one of ordinary skill in the art a method of evaluating the efficiency of a sterilization process using proteins described by Coustou *et al.*, Glover *et al.*, or Wickner *et al.* It is evident from Figure 1 of Safar *et al.* that prion proteins are still present in about the same quantity both before and after treatment. (See, Aigle Declaration, paragraph 7) Applicants respectfully suggest that alleging to the contrary constitutes impermissible hindsight.

3. The Examiner rejects claim 9 as allegedly unpatentable over Safar *et al.*, *Protein Science*, 1993, 2:2206-2216 in view of Coustou *et al.*, *PNAS* (1997), Glover *et al.*, *Cell* (1997) or Wickner, *Science* (1994) and further in view of Feldman *et al.*, "Compatibility of medical devices and material with low-temperature hydrogen perioxide gas plasma," (1997). Applicants respectfully traverse. Claim 9 is patentable under 35 USC 103(a) over Safar *et al.* in view of Coustou *et al.*, Glover *et al.* or Wickner *et al.* in further view of Feldman *et al.*

For the reasons provided above, Applicants submit that the method of claim 9 is not obvious over Safar *et al.* in view of Coustou *et al.*, Glover *et al.* or Wickner *et al.* in further view of Feldman *et al.* The teachings of Safar *et al.* that heat or chemical treatment may affect the ***conformation*** of a mammal prion protein do not teach or suggest a method of evaluating the efficiency of a sterilization process (e.g. using oxidizing agents such as hydrogen as a form of low-temperature gas plasma as in Feldman *et al.*) using proteins described by Coustou *et al.*,

Glover *et al.* or Wickner *et al.* It is evident from Figure 1 of Safar *et al.* that prion proteins are still present in about the same quantity both before and after treatment. (See, Aigle Declaration, paragraph 7) As such, the references, when combined, do not produce the presently claimed methods.

4. The Examiner rejects claims 9, 10 and 13 as allegedly unpatentable over Safar *et al.*, *Protein Science*, 1993, 2:2206-2216 in view of Coustou *et al.*, *PNAS* (1997), Glover *et al.*, *Cell* (1997) or Wickner, *Science* (1994) and further in view of Dresdner *et al.*, U.S. Patent 5,357,636. Applicants respectfully traverse. Claims 9, 10 and 13 are patentable under 35 USC 103(a) over Safar *et al.* in view of Coustou *et al.*, Glover *et al.* or Wickner *et al.* and further in view of Dresdner *et al.*

Similarly, for the reasons provided above, Applicants submit that the methods of claims 9, 10 and 13 are not obvious over Safar *et al.* in view of Coustou *et al.*, Glover *et al.* or Wickner *et al.* in further view of Dresdner *et al.* The teachings of Safar *et al.* that heat or chemical treatment may affect the ***conformation*** of a mammal prion protein do not teach or suggest a method of evaluating the efficiency of a sterilization process (e.g. using ozone or sodium hydroxide as in Feldman et al.) using proteins described by Coustou *et al.*, Glover *et al.* or Wickner *et al.* It is evident from Figure 1 of Safar *et al.* that prion proteins are still present in about the same quantity both before and after treatment. (See, Aigle Declaration, paragraph 7) As such, the references, when combined, do not produce the presently claimed methods.

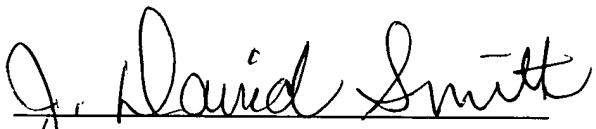
FEES

No additional fees are believed to be necessary. However, if any fees are due, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks in the file of the instant Application. Early and favorable action on the claims is earnestly solicited. If any issues may be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

By: 

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